DNA demethylation dynamics.

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Public Summary:
The significant impact of DNA methylation patterns on cell and organismal fate is perhaps most graphically exemplified in honeybees, in which differential DNA methylation determines whether the bee will be a worker or a queen (Kucharski et al., 2008). In mammals, DNA methylation has also long been considered integral to fundamental choices, including the long-term gene silencing that leads to genomic imprinting, X chromosome inactivation, suppression of transposable elements, and the establishment and maintenance of stable cellular identities (Bird, 2002; De Carvalho et al., 2010; Deaton and Bird, 2011; Goll and Bestor, 2005; Jaenisch and Bird, 2003). Yet, studies of cellular reprogramming by three approaches—nuclear transfer, cell fusion, and induced pluripotency by defined factors (i.e., iPSCs)—all demonstrate that ''fixed and stable'' differentiated cellular states can be radically altered (Jullien et al., 2011; Yamanaka and Blau, 2010). Concurrently, accumulating evidence has suggested that DNA methylation may be reversible in mammalian cells; however, knowledge of the requisite molecules and mechanisms underlying this process has been lacking. In this Perspective, we focus on recent reports that now identify enzymes capable of mediating DNA demethylation in mammalian cells. These findings raise the possibility that regulation by DNA methylation is at times quite dynamic, providing exciting insights into why reprogramming of cell fates is possible.

Scientific Abstract:
The discovery of cytosine hydroxymethylation (5hmC) suggested a simple means of demethylating DNA and activating genes. Further experiments, however, unearthed an unexpectedly complex process, entailing both passive and active mechanisms of DNA demethylation by the ten-eleven translocation (TET) and AID/APOBEC families of enzymes. The consensus emerging from these studies is that removal of cytosine methylation in mammalian cells can occur by DNA repair. These reports highlight that in certain contexts, DNA methylation is not fixed but dynamic, requiring continuous regulation.

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